PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZRC-MC-017	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/IN2004/000319	International filing date *(day/month/year)* 14.10.2004	Priority date *(day/month/year)* 14.10.2003
International Patent Classification (IPC) or national classification and IPC INV. C07D265/38 C07D279/26 C07D263/24 C07D209/86 C07D401/04 C07D265/36 C07D209/08 C07D279/16 C07D263/32 C07D495/04 C07D215/06 C07D213/30 C07D239/90 C07D207/32 C07D413/04 C07D409/04 C07D213/74 C07D239/56 C07D239/42 C07D405/04 C07D249/18 C07D235/06 C07D263/56 C07D277/64		
Applicant CADILA HEALTHCARE LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.04.2005	05.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Fritz, M Telephone No. +31 70 340-3024

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2004/000319

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-61	as originally filed

Claims, Numbers

1(part), 2-4, 5(part), 10-13	as originally filed
1(part), 5(part), 6-9	received on 02.09.2005 with letter of 29.08.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2004/000319

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8-11

because:

☒ the said international application, or the said claims Nos. claims 8-11 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,8-13
	No:	Claims	1-4,6-7
Inventive step (IS)	Yes:	Claims	5
	No:	Claims	1-4,6-13
Industrial applicability (IA)	Yes:	Claims	1-7,12-13
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 8-11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with re-spect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

The initial phase of the search revealed that many representatives of the compounds I are already known in the art. Furthermore claims 1-4,6-13 relate to an extremely large number of possible products und uses thereof, whereas support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found for only a very small proportion of the compounds claimed.

In the present case the claims so lack support and the application so lacks disclosure that a search over the whole scope claimed appeared meaningless; consequently the search was carried out only on that part of claims 1-4,6-13 referring to
compounds (I) in which
I, m = 1
B represents oxygen
Ar designates a divalent aromatic group
Y = COR_3 wherein R_3 is OH or unsubstituted alkoxy, aryloxy, aralkyloxy

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D7: WO 98/27109 A (WARNER-LAMBERT COMPANY; DOHERTY, ANNETTE, MARIAN; KALTENBRONN, JAMES,) 25 June 1998 (1998-06-25)
D11 US-B1-6 414 002 (CHENG PETER T ET AL) 2 July 2002 (2002-07-02)
D12 WO 01/21602 A (BRISTOL-MYERS SQUIBB COMPANY; CHENG, PETER, T., W; DEVASTHALE, PRATIK;) 29 March 2001 (2001-03-29)

The present application relates to compounds of the general formula (I) and representatives thereof (claims 1-5), pharmaceutical compositions thereof (claims 6-7) methods of treatment by administering the compounds (I) (claims 8-10), the use thereof as a medicament (claim 11) as well as processes for the preparation thereof (claims 12-13).

For the assessment of the present claims 8-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentabi-lity can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The following comments with regard to novelty and inventive step of claims 1-4 and 6-13 only refer to the subject-matter thereof which was actually searched (vide supra, Art. 17(2) PCT).

The following substances are representatives of the compounds (I) and thus detrimen-tal for the subject-matter of claims 1-4 and 6-7.

D7: Structural formula on p. 28. lines 18-24
Title cpd. of ex. 3, step 1
Title cpd. of ex. 3, step 2
Title cpd. of ex. 3, step 3

D7 is an accidental disclosure, as none of these documents reates to the use of the compounds described therein for the treatment of diabetes or related disorders.

The subject-matter of claims 5 and 8-13 is novel in the sense of Article 33(2) PCT.

As closest prior art can be regarded D11 or D12.

Both documents disclose substances which are representatives of the compounds (I) (excluded from the subject-matter claimed by a proviso and thus not detrimental for the novelty of the claims).

D11 and D12 refer to compounds which allegedly have the same pharmacological activities as the compounds (I).

The problem underlying the present application has to be formulated as to provide fur-ther substances that are suitable for the treatment of hyperlipidemia, diabetes or related disorders.

It is noted that there are neither in D11 nor in D12 pharmacological data showing that the compounds actually disclosed therein are useful in the treatment of diabetes or related disorders.

It has been demonstrated by the applicant by way of comparative tests that representatives of the compounds according to the present case are, unexpectedly, superior to the compounds disclosed in D11 / D12, those compounds of the subject-matter sear-ched which are actually novel cannot be considered obvious for the skilled man.

In this respect the following is noted:
The Applicant is entitled to claim all obvious modifications of what was described (cf. Guidelines C-III, 6.2); alternative variations have to be supported by a certain number of examples (s. Guidelines C-II, 4.9); in this case the breadth of the main claim represents a reasonable generalisation of what has been exemplified, so that it can be assumed that every compound falling within its scope actually provides a solution to the problem underlying the invention.

Non-limiting terms like "optionally substituted" (not followed by a concrete list of substituents precising this term) as well as "derivatives" as used in the product claims of the present application are, however, speculative in the sense of Article 33(3) PCT: They include a great variety of structural possibilities not yet explored by the applicant, the effect of which cannot be foreseen having regard to the problem underlying the present invention.

Non-limititing terms as cited above include
- chemical groups which are structurally so remote from those of the examples that the activity of molecules comprising them cannot be predicted within the limits of qualitative structure-activity-relationship considerations
- mutagenic and/or toxic groups
- known pharmacophoric groups with the same or a completely different activity which leads to hybrid molecules or bio-conjugates the actual biological activities of which are unpredictable,

i.e. it cannot be foreseen, whether those molecules provide a solution to the problem at all.

An inventive step in the sense of Article 33(3) PCT can therefore only be acknowledged for the subject-matter of claim 5.

Further objections:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art dis-closed in the documents D11-D12 is not mentioned in the description, nor are these documents identified therein.

It should be indicated in the description that cpd. 52 on p. 40 is not a representative of the compounds (I).

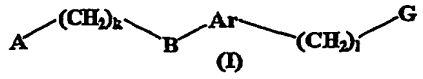
Several of the compunds listed in claim 5 (e.g. the last compound on p. 63) are not lon-ger within the scope of claim 1. Claim 5 which is formulated as being dependent from claim 1 does therefore not fulfil the requirements of Article 6 PCT.

Amended claims have been filed, but the description has not been adapted thereto which gives rise to an objection under Article 6 PCT.

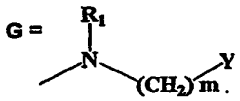
ZRC-MC-017

We claim

1. A compound of formula (I)

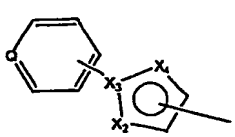


(I)



their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates wherein

'A' represents an optionally substituted group selected from heteroaryl which may be single or fused, or fused heterocyclyl groups, 'B' represents oxygen or sulfur; 'Ar' represents an optionally substituted divalent aromatic, heteroaromatic group, each of them may optionally be fused; R_1 represents hydrogen, optionally substituted groups selected from alkyl (linear or branched), alkenyl (linear or branched), alkynyl (linear or branched), aralkyl, aryloxycarbonyl, alkoxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, heteroarylcarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, hydroxyalkyl, alkoxy, alkylsulfonyl, arylthiocarbonyl, heteroarylsulfonyl, arylsulfonyl groups; k, l and m are integers independently ranging from 1-3; Y is COR_3 (where R_3 is OH or substituted or unsubstituted alkoxy, aryloxy, aralkyloxy, NH_2, aminoalkyl, amiodialkyl, aminoaralkyl, aminoalkylaralyl groups); $(CH_2)_k$, $(CH_2)_l$, $(CH_2)_m$, may be optionally substituted with one or more substituents selected from optionally substituted alkyl, haloalkyl, aryl, alkenyl, alkoxy, aryloxy, aralkoxy, alkoxycarbonyl, aryloxycarbonyl and the like; with the proviso that, 'A' does not represent



(Benzyl-{3-[2-(3,4-dihydro-2H-quinolin-1-yl)-ethoxy]-benzyl}-amino)-acetic acid and its pharmaceutically acceptable salts;

(Benzyl-{3-[2-(4-methanesulfonyloxy-phenyl)-ethoxy]-benzyl}-amino)-acetic acid and its pharmaceutically acceptable salts;

{Benzyl-[3-(2-phenoxazin-10-yl-ethoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;

{Benzyl-[3-(2-carbazol-9-yl-ethoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;

(Benzyl-{3-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzyl}-amino)-acetic acid and its pharmaceutically acceptable salts;

(Benzyl-{3-[2-(2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethoxy]-benzyl}-amino)-acetic acid and its pharmaceutically acceptable salts;

(Benzyl-{3-[2-(2,3-dihydro-benzo[1,4]thiazin-4-yl)-ethoxy]-benzyl}-amino)-acetic acid and its pharmaceutically acceptable salts;

{Benzyl-[3-(2-indol-1-yl-ethoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;

{Benzyl-[3-(3-phenothiazin-10-yl-propoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;

{Benzyl-[3-(3-methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;

[Benzyl-(3-{2-[2-methyl-5-(4-methylsulfanyl-phenyl)-pyrrol-1-yl]-ethoxy}-benzyl)-amino]-acetic acid and its pharmaceutically acceptable salts;

{(4-Methoxy-phenoxycarbonyl)-[4-(2-phenoxazin-10-yl-ethoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;

{(4-Methoxy-phenoxycarbonyl)-[4-(2-phenothiazin-10-yl-ethoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;

{(4-Methoxy-phenoxycarbonyl)-[4-(2-oxo-3-phenyl-oxazolidin-5-ylmethoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;

[(4-Methoxy-phenoxycarbonyl)-(3-{2-[2-methyl-5-(4-methylsulfanyl-phenyl)-pyrrol-1-yl]-ethoxy}-benzyl)-amino]-acetic acid and its pharmaceutically acceptable salts;
[[4-(Benzothiazol-2-ylmethoxy)-benzyl]-(4-methoxy-phenoxycarbonyl)-amino]-acetic acid and its pharmaceutically acceptable salts;
{(4-Methoxy-phenoxycarbonyl)-[4-(2-morpholin-4-yl-ethoxy)-benzyl]-amino}-acetic acid and its pharmaceutically acceptable salts;
[(4-Methoxy-phenoxycarbonyl)-(4-{2-[methyl-(4-nitro-phenyl)-amino]-ethoxy}-benzyl)-amino]-acetic acid and its pharmaceutically acceptable salts;
[(4-Methoxy-phenoxycarbonyl)-(3-{2-[2-methyl-5-(5-methyl-thiophen-2-yl)-pyrrol-1-yl]-ethoxy}-benzyl)-amino]-acetic acid and its pharmaceutically acceptable salts;
[[4-(Benzooxazol-2-ylmethoxy)-benzyl]-(4-methoxy-phenoxycarbonyl)-amino]-acetic acid and its pharmaceutically acceptable salts;

6. A pharmaceutical composition which comprises compounds of formula (I), as claimed in any preceding claims and a pharmaceutically acceptable carrier, diluent, excipients or solvate.

7. A pharmaceutical composition according to claim 6, in the form of a tablet, capsule, powder, granule, syrup, solution or suspension.

8. A method of preventing or treating diseases caused by hyperlipidaemia, hypercholesteremia, hyperglycemia, obesity, impaired glucose tolerance, leptin resistance, insulin resistance, diabetic complications, comprising administering an effective, non-toxic amount of compound of formula (I) as defined in any preceding claims to a patient in need thereof.

9. The method according to claim 8, wherein the disease is type 2 diabetes, impaired glucose tolerance, dyslipidaemia, hypertension, obesity, atherosclerosis, hyperlipidaemia, coronary artery disease, cardiovascular disorders and other diseases wherein insulin resistance is the underlying pathophysiologal mechanism.